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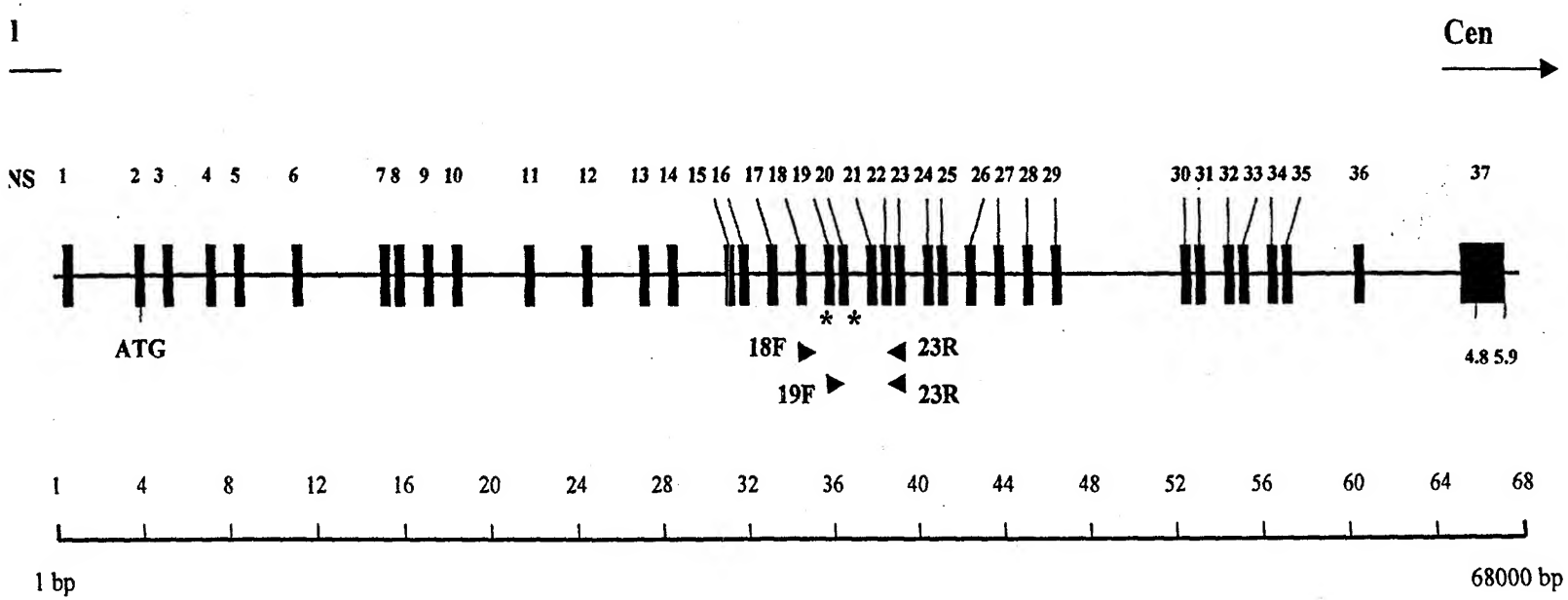
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Fig. 2a

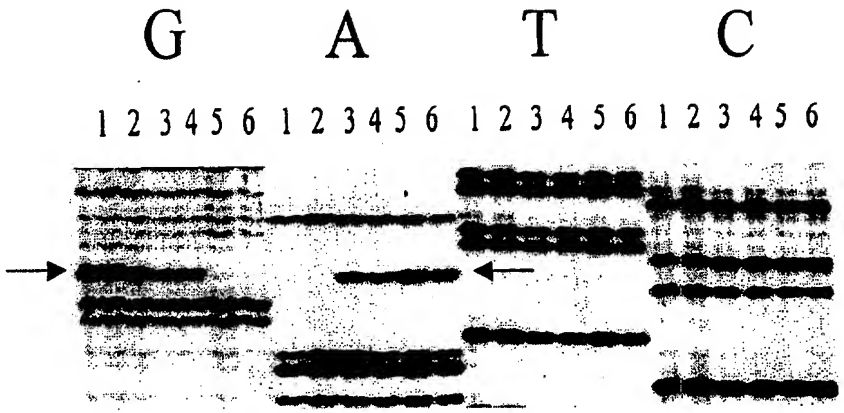

Fig. 2b

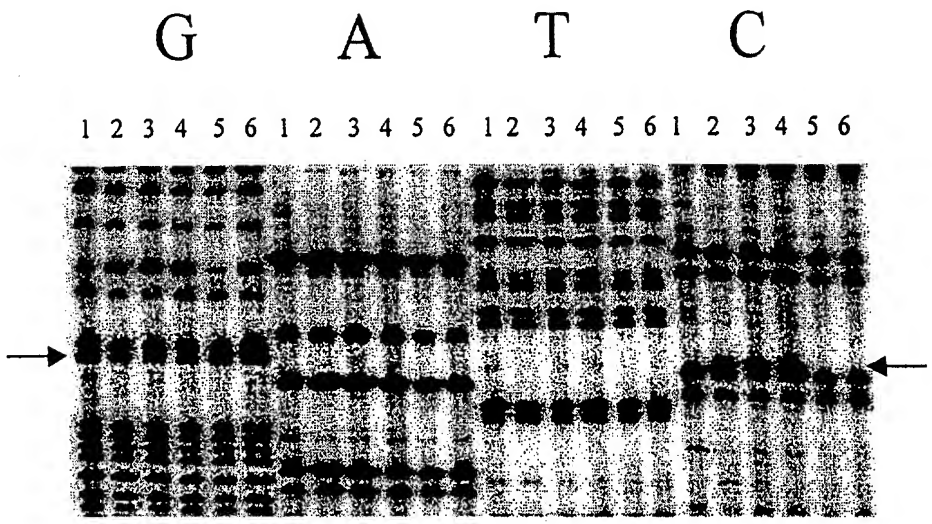

Fig. 2c

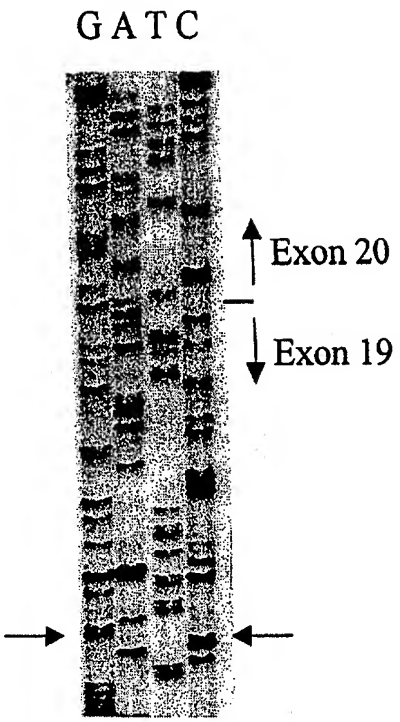

Fig. 3A

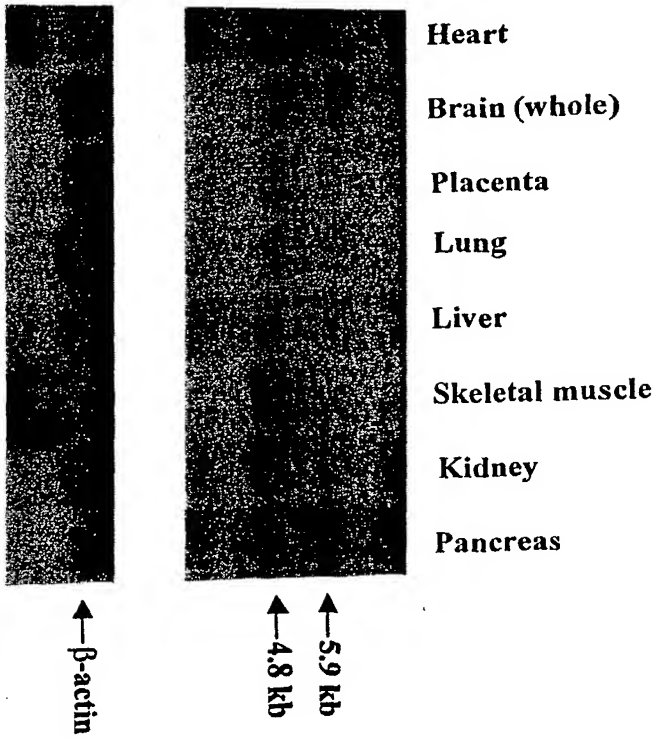

Fig. 3B

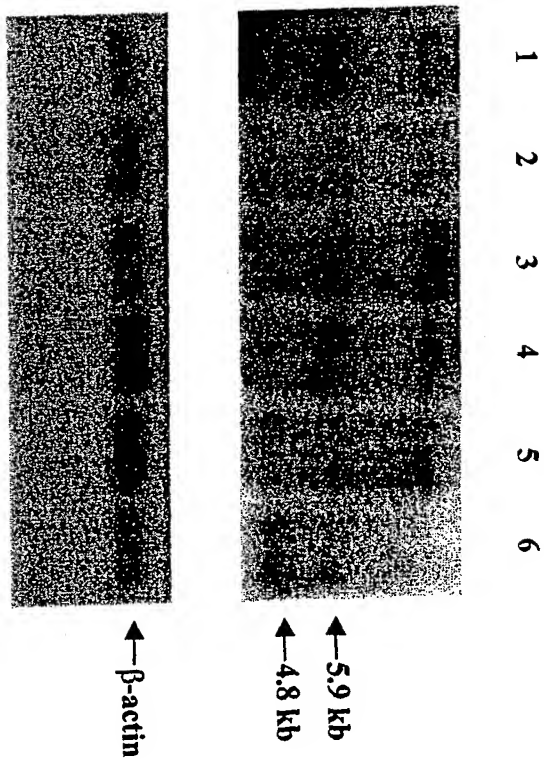

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FIG. 4A

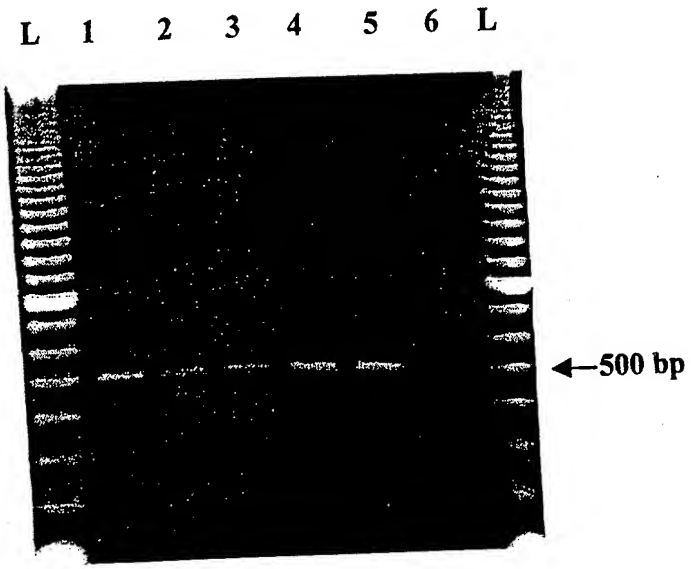
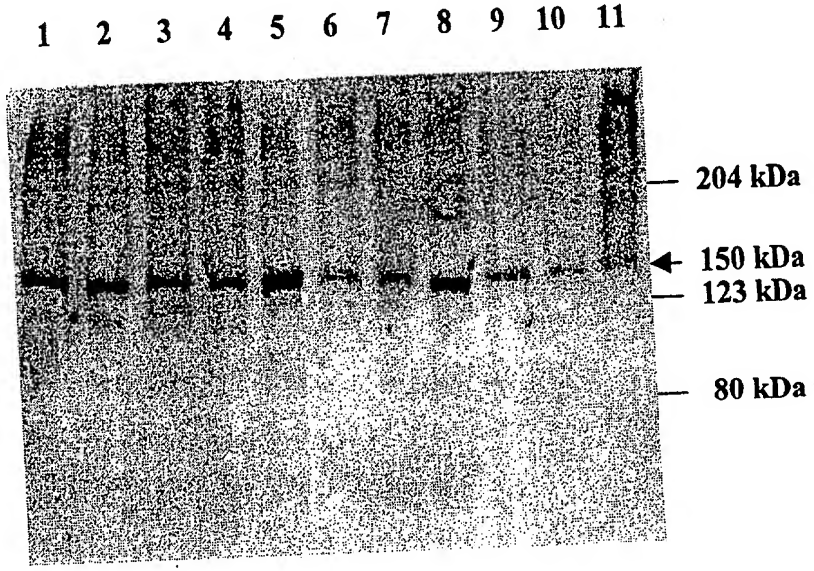


FIG. 4B



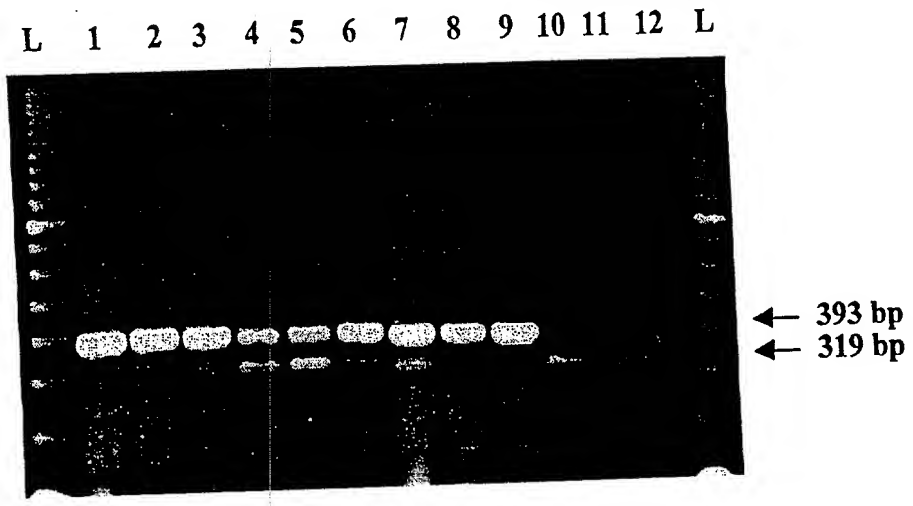


FIG. 5

FIGURE 6

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Art Unit: 1635

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Exhibit 1004, p. 1170 of 2702

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Exhibit 1006, p. 1866 of 2078

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Replacement Sheet

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FIGURE 7

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 961 ggctcggaag gtcagagtgt ggaaccgaga gtttgctttg cagtcaacca gtgagcctgt
1021 ggcaggactg ggaccagccc tggcttggaa accctcaggc agtttgattg catctacaca
1081 agataaaccc aaccagcagg atattgtgtt ttttgagaaa aatggactcc ttcatggaca
1141 ctttacactt cccttcctta aagatgaggt taaggtaaat gacttgctct ggaatgcaga
1201 ttcctctgtg cttgcagtct ggctggaaga ccttcagaga gaagaaagct ccattccgaa
1261 aacctgtgtt cagctctgga ctgttggaaa ctatcactgg tatctcaagc aaagtttatc
1321 cttcagcacc tgtgggaaga gcaagattgt gtctctgatg tgggaccctg tgaccccata
1381 ccggctgcat gttctctgtc agggctggca ttacctcgcc tatgattggc actggacgac
1441 tgaccggagc gtgggagata attcaagtga cttgtccaat gtggctgtca ttgatggaaa
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1561 actgctgttc ccacaccctg tgaatcaagt cacattctta gcacaccctc aaaagagtaa
1621 tgaccttgct gttctagatg ccagtaacca gatttctgtt tataaatgtg gtgattgtcc
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1801 tgtaaacccg ctgaaactag gccttctcac ttggattgaa gaagacgtct tcctggctgt
1861 aagccacagt gagttcagcc cccggtctgt cattcaccat ttgactgcag cttcttctga
1921 gatggatgaa gagcatggac agctcaatgt cagttcatct gcagcggtgg atggggtcat
1981 aatcagtcta tgttgcaatt ccaagaccaa gtcagtagta ttacagctgg ctgatggcca
2041 gatatttaag tacctttggg agtcaccttc tctggctatt aaaccatgga agaactctgg
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3001 ctatgacttt gatttggtcc tcatggtagc tgagaagtca cagaaggatc ccaaagaata
3061 tcttccattt cttaatacac ttaagaaaat ggaaactaat tatcagcggt ttactataga
3121 caaatacttg aaacgatatg aaaaagccat tggccacctc agcaaatgtg gacctgagta
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Figure 7
Continued

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3181 cttcccagaa tgcttaaact tgataaaaga taaaaacttg tataacgaag ctctgaagtt
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3301 gcaggagcac atgtatgagc cagcggggct catgtttgcc cgttgcggtg cccacgagaa
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3601 caaatataac agactggata ttatagaaac caacgtaaag ccttccattt tagaagccca
3661 gaaaaattat atggcatttc tggactctca gacagccaca ttcagtcgcc acaagaaacg
3721 tttattggta gttcgagagc tcaaggagca agcccagcag gcaggtctgg atgatgaggt
3781 accccacggg caagagtcag acctcttctc tgaaactagc agtgtcgtga gtggcagtga
3841 gatgagtggc aaatactccc atagtaactc caggatatca gcgagatcat ccaagaatcg
3901 ccgaaaagcg gagcggaaga agcacagcct caaagaaggc agtccgctgg aggacctggc
3961 cctcctggag gcactgagtg aagtggtgca gaacactgaa aacctgaaag atgaagtata
4021 ccatatttta aaggtactct ttctctttga gtttgatgaa caaggaaggg aattacagaa
4081 ggcctttgaa gatacgctgc agttgatgga aaggtcactt ccagaaattt ggactcttac
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4201 ggcatcttat cagcaacaga agacttcggt tcctgttctt gatgctgagc tttttatacc
4261 accaaagatc aacagaagaa cccagtggaa gctgagcctg ctagactgag tgactgcagt
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4501 atcattagca agacattaag ctttaaccat tatggcacca ttttgtgaga atgattgttc
4561 tttcacttgg gctgtttgag agcataatta tggtaatcat gagattaatg tttcatgatt
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4681 cggagaagat tacaatggct attagtgcta catttggtca aatgtaatca cttaaatagc
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5821 cttatattga aatatagtgc tcttgctttg gataactgta aagggaccca tgctgataga
5881 ctggaaatag aagtaaatgt gtttattgaa aaaaaaaaaa aaaa
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EP04785656.0/1760/2005

FIGURE 8

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   1 mrnlklfrtl efrdiqgpgn pqcfslrteq gtvligsehg lievdpvsre vknevslvae
  61 gflpedgsgr ivgvqdlldq esvcvatasg dvilcslstq qlecvgsvas gisvmswspd
 121 qelvllatgq qtlimmtkdf epileqqihq ddfgeskfit vgwgrketqf hgsegrqaaf
 181 qmqmhesalp wddhrpqvtw rgdgqffavs vvcpetgark vrvwnrefal qstsepvagl
 241 gpalawkpsg sliastqdkp nqqdivffek ngllhghftl pflkdevkvn dllwnadssv
 301 lavrledlqr ekssipktcv qlwtvgnyhw ylkqslsfst cgkskivslm wdpvtpyrlh
 361 vlcqgwhyla ydwhwttdrs vgdnssdlsn vavidgnrvl vtvfrqtvvp ppmctyqllf
 421 phpvnqvtfl ahpqksndla vldasnqisv ykcgdcpsad ptvklgavgg sgfkvclrtp
 481 hlekrykiqf ennedqdvnp lklglltwie edvflavshs efsprsvihh ltaassemde
 541 ehgqlnvsss aavdgviisl ccnsktksvv lqladgqifk ylwespslai kpwknsggfp
 601 vrfpypctqt elamigeeec vlgltdrcrf findievasn itsfavydef lllttthshtc
 661 qcfclrdasf ktlqaglssn hvshgevlrk vergsrivtv vpqdtklvlq mprgnlevvh
 721 hralvlaqir kwldklmfke afecmrklri nlnpiydhnp kvflgnvetf ikqidsvnhi
 781 nlfftelkee dvtktmypap vtssvylsrd pdgnkidlvc damravmesi nphkyclsil
 841 tshvkkttpe leivlqkvhe lqgnapsdpd avsaeealky llhlvdvnel ydhslgtydf
 901 dlvlmvaeks qkdpkeylpf lntlkkmetn yqrftidkyl kryekaighl skcgpeyfpe
 961 clnlikdknl ynealklysp ssqqyqdisi aygehlmqeh myepaglmfa rcgahekals
1021 afltcgnwkq alcvaaqlnf tkdqlvglgr tlagklveqr khidaamvle esaqdyeeav
1081 llllegaawe ealrlvykyn rldiietnvk psileaqkny mafldsqtat fsrhkkrllv
1141 vrelkeqaqq aglddevphg qesdlfsets svvsgsemsg kyshsnsris arssknrrka
1201 erkkhslkeg spledlalle alsevvqnte nlkdevyhil kvlflfefde qgrelqkafe
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1321 nrrtqwklsl ld
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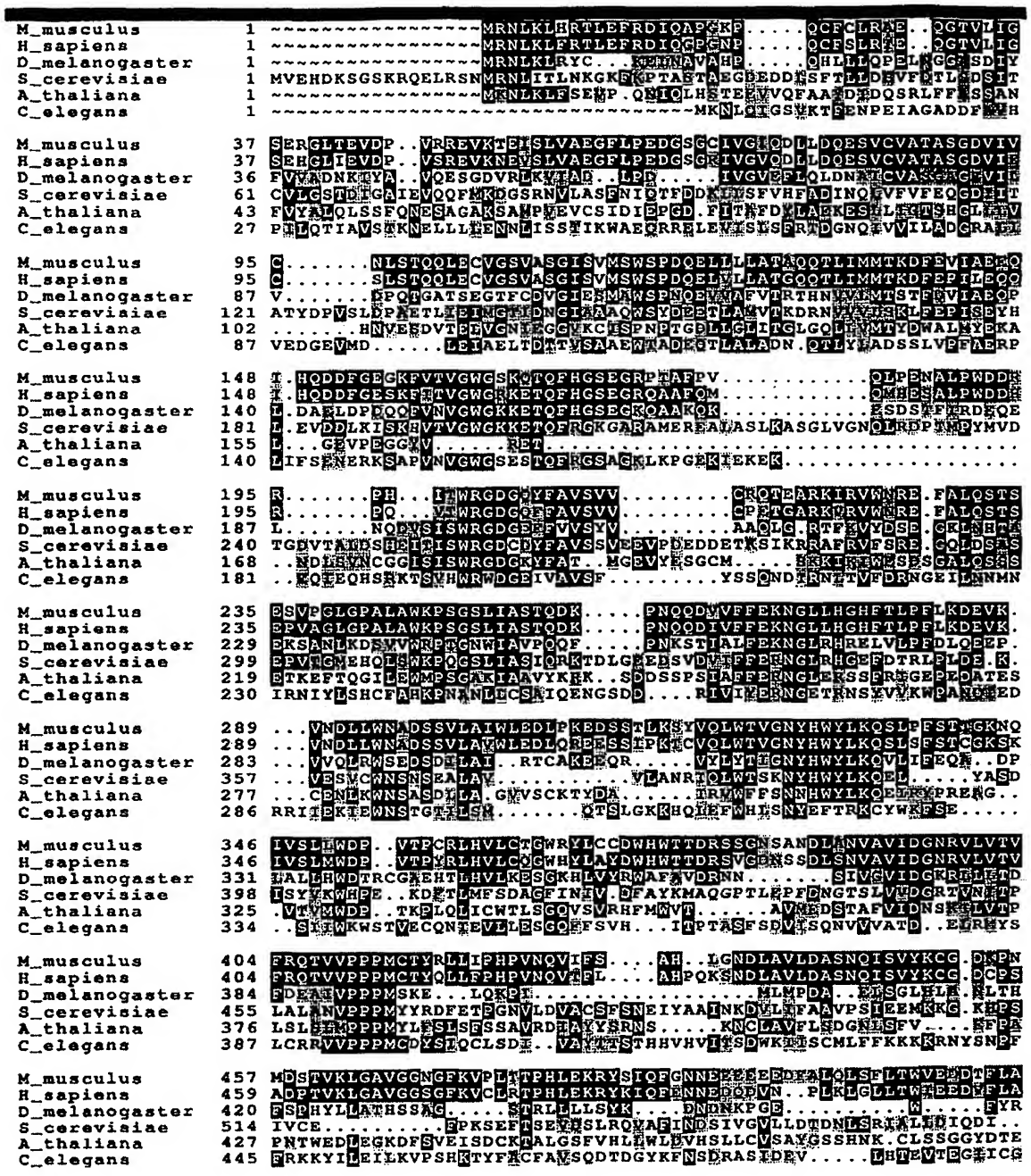

FIG. 1. Comparison of the amino acid sequence of Ikap across several species. Alignment of the amino acid sequence of Ikap (M_musculus) with that of *Homo sapiens* (H_sapiens), *Drosophila melanogaster* (D_melanogaster), *Saccharomyces cerevisiae* (S_cerevisiae), *Arabidopsis thaliana* (A_thaliana), and *Caenorhabditis elegans* (C_elegans). Black boxes indicate identical AA, while conserved AA residues are shown in gray. Asterisk (*) at AA position 696 for mouse and human proteins indicates the location of the heterozygous R696P mutation found in only 4 FD patients. Sequence alignments were made using Pileup and Boxshade commands from GCG Wisconsin Package V.9.0 (Madison, WI).

Figure 9

Figure 9
Continued

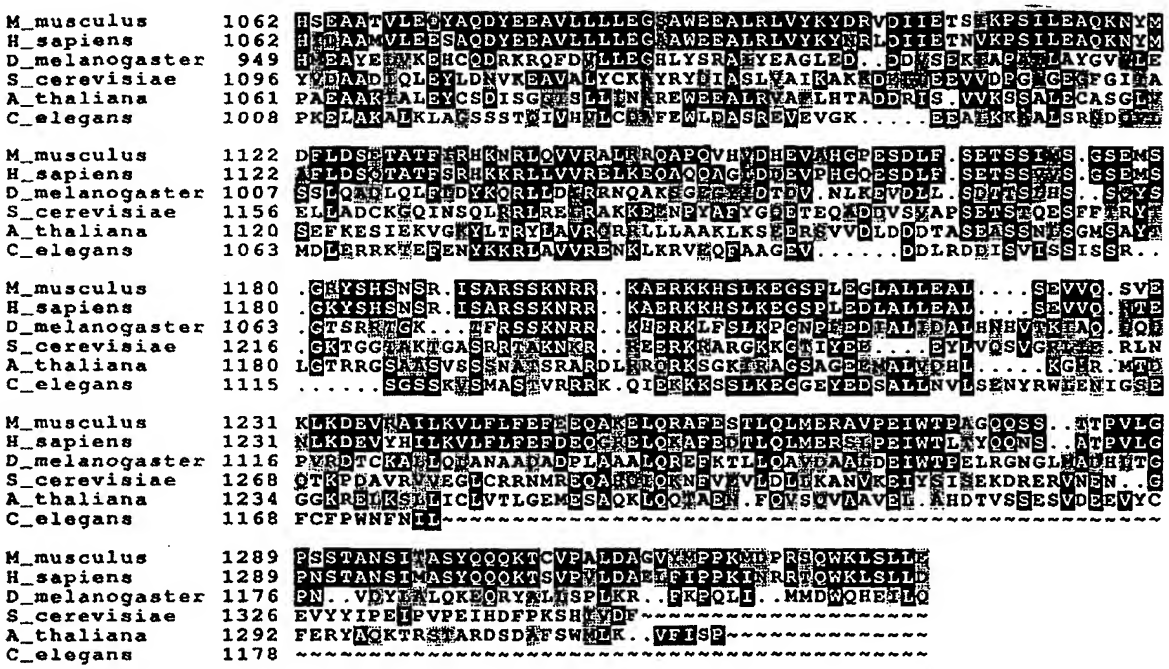

Figure 9
Continued

TABLE 2. COMPARISON OF THE NOVEL MOUSE *Ikbkap* GENE WITH MULTIPLE SPECIES HOMOLOGS

Species	*Gene name*	*No. of amino acids*	*Molecular weight (kDa)*	*% aa identity with M.m.*	*GenBank Accession No.*
Mus musculus (M.m.)	*Ikbkap*	1332	149.11	—	AF367244
Homo sapiens	*IKBKAP*	1332	149.11	80	AF153419
Drosophila melanogaster	*CG10535*	1213	138.21	32	AAF54670
Saccharomyces cerevisiae	*Elp1/Iki3p*	1349	152.99	29	AAB67278
Arabidopsis thaliana	Unknown	1308	146.63	27	BAB08695
Caenorhabditis elegans	Unknown	1177	134.80	24	AAF60430

Figure 10

PROMEGA 9-5-02

TABLE 1. MOUSE *Ikbkap* EXON AND INTRON BOUNDARIES

Exon	*Acceptor site*	*Donor site*	*Size (bp)*	*cDNA position*
1		AGgtgagcattcgcccg	129	1..129[a]
2	ttttttttccctcagAA	AAgtaggtcactgatgc	163	130..292[b]
3	tatgctttgtgaaagGT	AGgtaggtgtaaggcct	153	293..445
4	ttttctctgatgcagCT	AGgtaagctttgcactg*	82	446..527
5	acatgaactcctaagCT	AGgtaagcgtttcttgg	81	528..608
6	cttgaaaaactgtagGC	TGgtaaggcgggatgat	86	609..694
7	ggtgtctctcttcagCC	TGgtgtctctcttcagc*	97	695..791
8	ctacctcctttgcagAG	AAgtgagtgagcataaa*	91	792..882
9	aggttctgctttcagAC	AGgtaggggtcagagtt	124	883..1006
10	ttttgtcctaccagGT	TGgtatgacagcttgtg	94	1007..1100
11	tccctccacacacagTC	AAgtaagttgctgcgaa	231	1101..1331
12	cttttcattgtgtagAC	TGgtaagtggaagcagg	165	1332..1496
13	ttttttgttttctagGT	TCgtaagttcctaaata	100	1497..1596
14	ctaatatttgaacagGA	AGgtatcatggttcatc	189	1597..1785
15	tttttttgctttagTT	GGgtgaggatcagagtt	107	1786..1892
16	ttaatcttacaacagAG	AGgtgaatagacacggc	104	1893..1996
17	ttcatttctttgcagGA	AGgtatgtaggcttggt	54	1997..2050
18	tcttgcctgttgcagGT	AAgtaagctctcctata	106	2051..2156
19	cactggtatttttagTG	AGgtaagctgactcttc*	116	2157..2272
20	gggttttatttgagAT	AAgtaagtatttattct*	74	2273..2346
21	ttcctgtcctcacagAC	AGgtacactttgcgtct	79	2347..2425
22	tactttctttgatagGT	AGgtaagtattttgata*	80	2426..2505
23	tactgtggttcttagGG	AAgtgggtgctgtgtgt	138	2506..2643
24	cacttactacctcagGT	AGgtagagacctgcgcg*	86	2644..2729
25	cttaaactccaacagGA	AGgtatgtggagttgag*	149	2730..2878
26	aacttttttcctaggGA	TGgtaagggttttttt	124	2879..3002
27	ttttttttttttcagGA	AGgtatgtggtgggtta*	98	3003..3100
28	cgtctcttgtcacagGC	AGgtaagcagggccatt	202	3101..3302
29	ttgctgtcttttcagGA	AGgtgagctcctccccg	62	3303..3364
30	ctcttcccttgtcagGA	TGgtaaggaagctctga	63	3365..3427
31	tttcttccctcttagGT	AGgtgaggattacattt*	61	3428..3488
32	attatgcatcctcagCC	GGgtgagtgcctccaaa*	114	3489..3602
33	gttcatcttctctagAT	GCgtacgtacgagacct*	112	3603..3714
34	tgtaatttctgacagGA	AGgtatggcttcagtgc	128	3715..3842
35	ccatttcttctctagAT	CGgtaagcttcctcaga	155	3843..3997
36	ctgttttctgcttagGT	CGgtgtactgctcgttc	76	3998..4073
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Figure 11

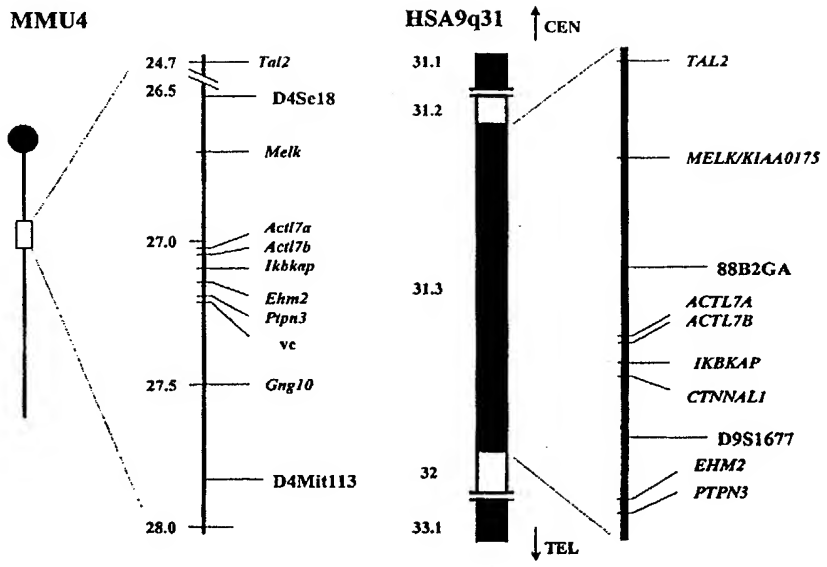

Figure 12

Sheet 9 of 9 Replacement